ORIGINAL ARTICLE

High prevalence and antimicrobial resistance of urinary tract infection isolates in febrile young children without localizing signs in Taiwan

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Abstract *Background:* Antimicrobial susceptibility and prevalence of pediatric urinary tract infection (UTI) is very useful for pediatricians in selecting effective antibiotics in time to improve outcomes in patients. This study aimed to determine the prevalence rate, bacterial distribution, and antimicrobial susceptibility of UTI in febrile young children at a teaching hospital in northern Taiwan.
Methods: From January 2011 to December 2011, all urinary isolates from suspected cases of UTI in febrile young children aged from 1 day to 36 months visiting the Pediatric Emergency Room of Chang Gung Children's Hospital, Taoyuan, Taiwan were identified by conventional methods. Antibiotic susceptibility was determined according to the Clinical and Laboratory Standards Institute.
Results: A total of 5470 (78%) from 7009 eligible children were enrolled in the study, and 619 (11.3%) had a diagnosis of UTI. The most prevalent bacterium was *Escherichia coli* (68%) followed by *Klebsiella pneumoniae* (8.1%) and *Proteus mirabilis* (6.8%). Ampicillin, piperacillin, and trimethoprim-sulfamethoxazole (TMP-SMX) showed a higher resistance rate in the three predominant bacteria. All tested bacteria showed higher resistance to ampicillin (79.3%) and TMP-SMX (44.1%), and lower resistance to cefazolin (17.7%) and gentamicin (13.0%). Fourteen

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percent of the isolates produced extended spectrum β-lactamase (ESBL), among which 93.33% were *E. coli* isolates.

Conclusion: The overall prevalence of UTI in this study was higher than previously reported in febrile children. Higher antimicrobial resistance was found in ampicillin and TMP-SMX. Among commonly used antibiotics, cefazolin and gentamicin are recommended to treat UTI in febrile children aged < 3 years without localizing signs.

Introduction

The true incidence of urinary tract infection (UTI) in febrile young children (≤ 3 years old) is difficult to estimate, particularly because those with UTI may only have fever without specific symptoms or signs.

UTI is a common cause of fever and a frequent reason for referral to the emergency department and hospitalization, particularly in infancy.[1] UTI is present in ∼1.8−13.6% of febrile infants and in ∼2−4.5% of febrile children aged < 5 years.[2−8] However, the prevalence rate of UTI in young children in Taiwan has never been reported.

UTI may present no urinary symptom or sign, and a delay in diagnosis and treatment may occur. In infants and young children aged < 3 years with unexplained fever, the degree of toxicity, dehydration, and ability to retain oral intake must be assessed carefully. The prognosis is usually favorable, but relies on timely administration of appropriate initial antimicrobial treatment.[8,9] Appropriate treatment requires information regarding the susceptibility patterns of the current bacteria in order to give effective antibiotics in time.[8−10] Although current antibiotic susceptibility of *Escherichia coli* has been reported,[11] no additional data are available regarding the overall uropathogens and their antibiotic susceptibilities. How to select effective antibiotics for treating current UTIs still remains unknown.

The present study was performed to determine the prevalence rate of UTI in patients aged < 3 years and the uropathogens in the emergency room of a tertiary pediatric medical center, examine their antibiotic susceptibility, and determine the appropriateness of the empirical antibiotics used.

Materials and methods

Study design

The study population consisted of patients attending the pediatric emergency department (PED) at a university teaching children's hospital in northern Taiwan between January 2011 and December 2011. A retrospective electronic chart review of medical records was performed. All infants aged ≤ 3 years presenting with fever (rectal temperatures ≥ 38°C by history or in the PED) were eligible for enrollment in the study. Infants were excluded if they had received antibiotics within 48 hours of PED presentation or if they had a definite source of fever on

examination. Clinical and laboratory data of all enrolled children were collected retrospectively from the electronic medical records. We recorded data on sex, age, underlying disorders, previous hospitalizations, previous antibiotic use, and results of urine culture.

Ethics statement

The project was reviewed and approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital, Taoyuan, Taiwan (IRB No. 102-0498B).

Inclusion criteria

Patients with positive urinary cultures were included. The method of urine sample collection for urine culture was clean-catch urine collection using a bag after thorough skin sterilization.[12−14] A good correlation has been proved between the results of a urine culture obtained using this method and by suprapubic bladder aspiration.[15] A positive culture was defined as follows: growth of a single urinary tract pathogen with at least > 10^5 colony-forming units (CFU)/mL in urine specimens.[11−16] Patients with underlying renal disease, recurrent UTI, or contamination were excluded.

Antibiotic susceptibility testing

Antibiotic susceptibility was determined using standard techniques.[17] Isolates in the "intermediate" category were deemed "resistant" in this study. Antimicrobial susceptibility was determined using the disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) standards.[18] Extended spectrum β-lactamase (ESBL)-producing organisms were screened and confirmed according to the method suggested by the CLSI.[18]

Statistical analysis

Data were recorded and entered into a database. Analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). The Student t test, the Chi-square test, or Fisher exact test was used when appropriate to compare proportions. All statistical analyses were two-sided, and significance was set at $p < 0.05$.

Results

Over the study period from January 1, 2011 to December 31, 2011, a total of 19,818 patients aged < 3 years visited the PED, and 7009 children fulfilled the criteria of fever. However, 1539 children were excluded due to having received antibiotic agents or the identification of any other reasons for fever in addition to UTI. Urine samples were collected from 5470 febrile children. A total of 619 patients whose urine samples met the definition of positive urine culture were finally enrolled in the study.

Table 1 compares prevalence among patients of different sex and age, including those aged < 1 year, between 1 year and 2 years, and between 2 years and 3 years. The mean age of the whole study group was 9.3 ± 8.3 months old. Overall prevalence in febrile patients aged < 3 years was 11.3%. Prevalence of febrile patients aged < 1 year (12.3%) was significantly higher than that of febrile patients aged 2−3 years (10%) and 1−2 years (8%; $p < 0.001$). In febrile patients aged < 1 year, boys had significant higher prevalence (14%) than girls (10.6%; $p = 0.004$). By contrast, girls had significant higher prevalence than boys in febrile patients aged 1−2 years ($p = 0.001$) and 2−3 years ($p = 0.005$).

The microorganisms were isolated in the 619 episodes of UTI in children. E. coli (68%), Klebsiella pneumoniae (8.1%), Proteus mirabilis (6.8%), and Enterobacter faecalis (4%) infection were the most prevalent bacteria in our patients. Twelve infections (2%) were caused by Pseudomonas aeruginosa. E. coli accounted for ~73.5% of cases in the 1-year-old age group, which was significantly higher than the incidences in the other age groups ($p = 0.001$). The frequencies of K. pneumoniae and P. mirabilis increased by not less than 1.4−2.8-fold in the 1−2-year-old and 2−3-year-old groups, respectively. The frequency and distribution of the different microorganisms are summarized in Table 2.

Table 3 shows the resistance of the three predominant pathogens to various antimicrobial agents. More than 70% of E. coli, K. pneumonia, and P. mirabilis were susceptible to most antibiotics, including cephalosporines (cefazolin, cefuroxime, ceftriaxone, and ceftazidime), aminoglycosides (gentamicin and amikacin), piperacillin-tazobactam (Tazocin), ciprofloxacin, and imipenem.

Among the antibiotics, amikacin and imipenem showed the widest coverage against E. coli isolates (100%), followed by Tazocin (98.6%). Moreover, the fluoroquinolones showed high potency against E. coli (91%). Klebsiella

isolates showed high susceptibility to imipenem (100%) followed by fluoroquinolones (98%), amikacin (94%), ceftazidime (92%), and ceftriaxone (92%). Among the β-lactam antibiotics, imipenem showed the widest coverage against Gram-negative isolates (100%). This was followed by amikacin and ciprofloxacin.

However, three antibiotics were more resistant to E. coli: 82.9% of the strains were resistant to ampicillin, 77.9% to piperacillin, and 48% to trimethoprim-sulfamethoxazole (TMP-SMX). Four antibiotics were more resistant to K. pneumonia: 98% of strains were resistant to ampicillin, 44% to piperacillin, 26% to cefazolin, and 22% to TMP-SMX. Two antibiotics were more resistant to P. mirabilis: 67% of strains were resistant to ampicillin and 38.1% to TMP-SMX. Resistance to third-generation cephalosporins was mostly due to the presence of ESBL. ESBLs were found in 15 patients (E. coli, $n = 14$; K. pneumoniae, $n = 1$).

Table 4 shows resistance of the four most commonly used antibiotics for treating UTIs in the three age groups. More than 40% resistance to ampicillin and TMP-SMX was found in the data of all age groups. A higher rate of resistance to ampicillin was found in data of the 2−3-year-old group than in that of the < 1-year-old group ($p = 0.035$). Resistance to cefazolin and gentamicin were significantly lower in data of the < 1-year-old group compared with that of the 1−2-year-old group (cefazolin: $p < 0.001$, gentamicin: $p = 0.038$).

Discussion

UTI is present in approximately 1.8−13.6% of febrile infants and ~2−4.5% of febrile children aged < 5 years.[2−4] The overall rate of UTI observed in this study was 11.3% in febrile children aged < 3 years. Higher rates in the younger age groups are seen in our study. An important difference is the high proportion of uncircumcised boys in Taiwan. In a recent Taiwanese study, the observed rate of UTI was 19% among 94 febrile uncircumcised male infants aged < 8 weeks.[19] In this study, the prevalence rates of UTI in girls aged < 1 year (10.6%) and between 1 year and 2 years (11.7%), and in boys aged < 1 year (14%) were higher than those in other reports (6.5%, 8.1%, and 3.3%, respectively).[20,21] This latter difference may have been due to the lower rate of circumcised boys in Taiwan compared with the United States. Wiswell and Roscelli[22] reported a 10-fold increase in the incidence of UTI in uncircumcised compared with circumcised male infants during the 1st year of life. If young children with suspected UTI are assessed as toxic,

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Table 1 Comparison of prevalence of urinary tract infection among children of different age and sex

Age (y)	Male No./total (%)	Female No./total (%)	p (male vs. female)	Total No./total (%)
<1	269/1956 (14)	199/1863 (10.6)	0.004	468/3819 (12.3)
1−2	43/679 (6.3)	58/495 (11.7)	0.001	101/1274 (8)
2−3	19/271 (7)	31/206 (15)	0.005	50/477 (10)
P (among age)	<0.001	0.158		<0.001
Overall	331/2906 (11.4)	288/2564 (11.2)	0.854	619/5470 (11.3)

Table 2 Comparison of bacteria isolated from patients with urinary tract infection in different age groups

Bacteria	Age group				p
	< 1 y	1–2 y	2–3 y		
Escherichia coli	344 (73.5)	52 (51.4)	25 (50)	421 (68)	0.001
Klebsiella pneumoniae	33 (7)	10 (9.9)	7 (14)	50 (8)	NS
Proteus mirabilis	25 (5.3)	10 (9.9)	7 (14)	42 (6.8)	NS
Enterococcus faecalis	17 (3.6)	5 (5)	1 (2)	23 (4)	NS
Morganella morganii	6 (1.3)	10 (9.9)	3 (6)	19 (3)	NS
Citrobacter species	11 (2.4)	3 (3)	1 (2)	15 (2)	NS
Escherichia coli ESBL	11 (2.4)	2 (2)	1 (2)	14 (2)	NS
Pseudomonas aeruginosa	4 (0.9)	4 (4)	4 (8)	12 (2)	NS
GBS	9 (1.9)	3 (3)	0	12 (2)	NS
Yeast	4 (0.9)	1 (1)	0	5 (0.8)	NS
Enterobacter cloacae	3 (0.6)	1 (1)	1 (2)	5 (1)	NS
Klebsiella pneumoniae ESBL	1 (0.2)	0	0	1 (0.2)	NS
Total	468 (75.6)	101 (16.3)	50 (8.1)	619	

Data are presented as *n* (%).
ESBL = extended spectrum β-lactamase; GBS = group B Streptococci ; NS = nonsignificant.

dehydrated, or unable to retain oral intake, initial antimicrobial therapy should be administered parenterally and hospitalization should be considered. Therefore, studies to increase our knowledge about the types of pathogen responsible for UTIs and their resistance patterns to antibiotic drugs are very important to help clinicians choose the appropriate empirical treatment.[23]

The results of the present study indicated the antibiotic susceptibility of uropathogen isolates responsible for UTI in different age groups of young children. UTIs are one of the most common types of bacterial infection encountered by both general practitioners and hospital doctors. Infants and children aged < 3 years with unexplained fever are cause for particular concern. UTI may cause few recognizable signs or symptoms other than fever, and has a greater potential for renal damage than in older children.[21]

This study shows the distribution and antibiotic susceptibility of microbial species isolated from infants and children aged < 3 years with community-acquired UTIs in a population in northern Taiwan. This study provided valuable laboratory data and allowed comparison of the situation in Taiwan with that in other countries. In the present study, *E. coli* was the most common pathogen isolated, which corresponds to the data obtained in other studies.[23–27] *K. pneumoniae* and *P. mirabilis* were the second and third most common pathogens, with rates of 8.3% and 7%, respectively. In the present study, only 12 infections (1.9%) were caused by *P. aeruginosa*, which was significantly lower than the rates in other reports (2.9–8%).[28–31]

The main differences between our results and those of studies conducted in Western countries were the resistance patterns of *E. coli*. *E. coli* and *Klebsiella* isolates in our study showed different resistance rates to ampicillin (82.9% and 98%, respectively), whereas for TMP-SMX and piperacillin, *E. coli* were more resistant (48% and 78%, respectively) than *K. pneumoniae* (22% and 44%, respectively) in

Table 3 Antimicrobial resistance of the three predominant urinary pathogens

	Escherichia coli N = 421		*Klebsiella pneumoniae* N = 50		*Proteus mirabilis* N = 42	
	No.	Resistance (%)	No.	Resistance (%)	No.	Resistance (%)
Ampicillin	349	82.9	49	98	28	67
Gentamicin	59	14	7	14	6	14.3
Cefazolin	67	15.9	13	26	6	14.3
Piperacillin	328	77.9	22	44	7	16.7
TMP-SMX	203	48.2	11	22	16	38.1
Amikacin	0	0	3	6	0	0
Ciprofloxacin	38	9	1	2	1	2.4
Cefuroxime	25	5.9	4	8	2	4.8
Tazocin	6	1.4	4	8	0	0
Ceftriaxone	23	5.5	4	8	0	0
Ceftazidime	19	4.5	4	8	0	0
Imipenem	0	0	0	0	0	0

TMP-SMX = trimethoprim-sulfamethoxazole.

Table 4 Comparison of resistance to the four most common antimicrobial agents for treating urinary tract infections among different age groups

	< 1 y	1–2 y	2–3 y	p (among the 3 age groups)	≤ 3 y
Ampicillin	355/455 (78.0)	75/94 (79.8)	42/46 (91.3)	0.105	472/645 (79.3)
Cefazolin	59/410 (14.4)	26/80 (32.5)	9/40 (22.5)	<0.001	94/530 (17.7)
Gentamicin	48/427 (11.2)	17/88 (19.3)	8/47 (17.0)	0.084	73/562 (13.0)
TMP-SMX	177/424 (41.7)	46/85 (54.1)	21/44 (47.7)	0.352	244/553 (44.1)

Data are presented as *n/N* (%).
TMP-SMX = trimethoprim-sulfamethoxazole.

this study. Rates of resistance to ampicillin are high in *E. coli* (82.9%), *K. pneumoniae* (98%), and *P. mirabilis* (67%). The resistance rates to ampicillin increased in comparison to previous analyses.[29–31] Pape et al[31] reported 100 children with community UTI. The resistance rates to ampicillin were 69% in *E. coli*. Ladhani and Gransden[29] studied 1774 children with UTI and reported rates of resistance to ampicillin in *E. coli* (51.1%), *K. pneumoniae* (100%), and *P. mirabilis* (15.2%). The extensive use of these drugs explains the high selection pressure for resistant bacteria. Our rate of uropathogens resistant to TMP-SMX (44.1%) was higher than anticipated. Allen et al[32] reported a rate of resistance to TMP-SMX of 31% in children (inpatients and outpatients). In this study, the rate of TMP-SMX resistance in *E. coli* was 48.2% lower than reported previously by Wu et al.[33] However, the resistance rate increased in the older age group. Furthermore, *E. coli* showed increases in resistance rate to third-generation cephalosporins in Taiwan. ESBLs were found in 15 patients (*E. coli*, n = 14; *K. pneumoniae*, n = 1). Of our *E. coli* isolates, 3.2% were ESBL producers, followed by 1.9% of *K. pneumoniae*. The high level of multidrug resistance may have been due to the production of ESBLs by these isolates.[23,34–36]

The initial choice of antibacterial therapy is based on knowledge of the predominant pathogen in the patient's age group, antibacterial sensitivity patterns in the practice area, the clinical status of the patient, and the opportunity for close follow up. The use of an inappropriate antibiotic will delay effective treatment and increase the risks of urosepsis and renal scarring.[21] The current American Academy of Pediatrics guideline for management of UTIs in febrile infants and young children suggests to give oral or parenteral (then changed to oral) antibiotics for 7–14 days.[16] Ceftriaxone, cefotaxime, ceftazidime, gentamicin, tobramycin, and piperacillin were drugs of choice for parenteral therapy.[16] By contrast, amoxicillin-clavulanate, sulfonamide (trimethoprim-sulfamethoxazole or sulfisoxazole), or cephalosporin (cefixime, cefpodoxime, cefprozil, cefuroxime axetil, or cephalexin) was recommended as an oral agent for treating UTI.[16] In Taiwan, use of ampicillin and TMP-SMX as a single agent for empirical treatment of a suspected UTI would not cover the majority of urinary pathogens according to this study. Amikacin is suitable in all age groups. Cefazolin and gentamicin are effective therapeutic agents for pediatric UTIs,[33] and are recommended as a first-line therapy in cases of uncomplicated UTI. We found lower resistance rates to cefazolin and gentamicin in UTI in the < 1-year-old group. The resistance rate increased in the older age groups. The third generation cephalosporin

should be reserved for serious or critical cases to prevent bacterial resistance. Our results also indicated that the resistance rate of ampicillin was higher in the 2–3-year-old group. Pediatric doctors must be aware of the resistance patterns of uropathogens in their practice area and prescribe empirical antibiotics. The increasing rates of resistance of *E coli* to ampicillin, piperacillin, and TMP-SMX limit their use in symptomatic UTI.

In conclusion, regional and demographic differences in the susceptibility patterns of urinary pathogens mandate local, population-specific surveillance to choose the appropriate empirical pharmacotherapy for UTIs in children. We suggest that empirical antibiotic selection should be done based on local prevalence of bacterial organisms and antibiotic sensitivities rather than on universal guidelines. This study revealed increasing resistance rates of *E. coli* and production of ESBL among patients with UTI aged < 3 years. Although cefazolin and gentamicin remain good choices for most patients in our community, we should identify those pediatric patients in the emergency department who are at increased risk of infection with resistant pathogens and require an alternative antibiotic. This study will be useful for pediatric doctors in Taiwan to improve appropriate empirical treatment.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

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